Research Article

How Much Does Body Mass Index Affect Serum Carcinoembryonic Antigen Concentration?

Feng Li, Zhenhai Shen, Yun Lu, Ling Wang, and Wenjun Song

Abstract

Background: As the effect of obesity on serum carcinoembryonic antigen (CEA) concentration and mass is uncertain, we designed the study in context of Chinese healthy males with no clinical evidence of any cancer.

Methods: Of note, 1,915 healthy males were retrospectively collected, with ages ranging from 18 to 84 years. Two equations, a body surface area (BSA)–based and a hematocrit-based, were applied, respectively, for plasma volume and CEA mass calculation. Multivariate linear and logistic regression models were used to detect the associations of CEA concentration, and the two estimates of CEA mass with body mass index (BMI); possible confounding factors, including age, leucocyte count, and smoking status, were adjusted.

Results: CEA concentration significantly decreased with increasing BMI ($P < 0.001$); however, CEA mass remained consistent or increased by using the BSA- or hematocrit-based equation. A screening level of CEA 5.0 ng/mL in normal-weight men was found to correspond to 4.52 ng/mL in overweight and obese men.

Conclusions: CEA may be affected in obese individuals by several factors, including but not limiting to hemodilution, inflammatory conditions, and insulin resistance. The relationship between CEA concentration and BMI might be highly dependent on which factor or factors have been predominant.

Impact: The BMI status of participants should be taken into account during assessment of serum CEA levels in healthy males. *Cancer Epidemiol Biomarkers Prev; 23(3); 555–60. ©2014 AACR.*

Introduction

The worldwide prevalence of obesity has increased rapidly in the past two decades, with more than doubled between 1980 and 2008 according to the World Health Organization. Increased body mass index (BMI) has been linked to death from many cancers (1). The fact that increased BMI negatively affects the diagnostic precision through assessment of serum concentrations of soluble tumor markers, might contribute, at least partly, to the increased risk of certain cancer-caused death in obese persons (2).

Carcinoembryonic antigen (CEA) is one of these serologic markers of malignant tumors, which is overexpressed in adenocarcinomas in many organs. A recent study (3) has also shown that higher BMI is associated with lower CEA in patients with colorectal cancer, and that hemodilution from increased plasma volume may be responsible for the decreased serum CEA levels. However, this theory has not been confirmed in any healthy cohorts.

Therefore, we designed a study in healthy Chinese males, to explore whether larger plasma volumes in obese men are associated with lower CEA concentrations. In consideration of the lack of "golden criterion" for noninvasive plasma volume estimation, two plasma volume estimates were applied in the study: one is a commonly used equation based on height and weight; another is widely applied for drug administration based on weight and hematocrit. The influence of BMI status on interpretation of CEA value was additionally quantified.

Materials and Methods

Participants selection

The collected records of 2,359 consecutive healthy males presenting at our unit for health management from October 2012 to December 2012 were reviewed retrospectively. Analyses were confined to men with BMI > 16 kg/m², and a hematocrit from 0.37 to 0.54 ($n = 2,304$), as values out of these ranges are likely to represent data errors or to reflect underlying disease processes. We excluded men with missing BMI data ($n = 54$), no recorded hematocrit ($n = 90$) or CEA concentration ($n = 157$), and no data of smoking status ($n = 74$) or lack of the fecal occult blood test ($n = 82$). Participants with a history of inflammatory bowel disease ($n = 17$), or renal or liver insufficiency ($n = 26$) were additionally excluded. Abnormal liver function was defined as serum aspartate aminotransferase or alanine aminotransferase concentrations >80 IU/L. Abnormal kidney function was defined as serum creatinine concentration >133 μmol/L (1.5 mg/dL).

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History inquiry, physical examination, chest X-ray, abdominal ultrasound, and the above mentioned laboratory tests were performed in all the remaining subjects. People with abnormal results were arranged for follow-up tests in local hospitals. We provided follow-up telephone calls to the participants in April 2013. People with cancers ($n = 12$) diagnosed previously or during follow-up were further excluded: colorectal cancer ($n = 3$), gastric cancer ($n = 1$), lung cancer ($n = 3$), kidney cancer ($n = 2$), and thyroid cancer ($n = 3$). There were overlaps among these missing data. The remaining 1,915 males were included in the present analysis. Our local Institutional Review Board approved the survey before it was conducted.

BMI was calculated as weight in kilograms divided by height in meters squared. Participants were weighed with emptied pockets and without shoes. Standing height was measured using a fixed stadiometer with a vertical backboard and a moveable headboard. Subjects were divided into three BMI categories of ≤ 22.9, 23–27.5, and ≥ 27.5 according to the new Asian classification (4).

Subjects who had quit smoking for 1 month or less and those who had quit for more than 1 month before the time of the health screening were considered to be, respectively, current and former smokers, and those without a smoking history were considered to be never smokers.

The hematocrit was measured on a Hematology Analyzer (Beckman Coulter Gen-S System 2); alanine aminotransferase, aspartate aminotransferase, and serum creatinine on a Hitachi 7600 modular chemistry analyzer; serum CEA concentration on a Beckman Coulter DXI 800 Immunoassay Analyzer; fecal occult blood by the colloidal gold method using an anti-human hemoglobin monoclonal antibody (fecal occult blood gold gel strip; Beijing WanHuaPuMan Bio-Engneering Co., Ltd); chest X-ray by Digital Diagnost System (Philips), and abdominal ultrasound exam by the ultrasound system (Philips IU 22 or GE Healthcare LOGIQ E9). All the above assessments were measured by qualified staffs at our health management center.

Two plasma volume equations were applied as follows (5–8):

1. Body surface area (BSA)-based equation:

$$\text{Body surface area (m}^2) = \text{body weight (kg)}^{0.425} \times \text{height (m)}^{0.725} \times 0.2025$$

$$\text{Plasma volume (L)} = \text{body surface area (m}^2) \times 1.670$$

2. Hematocrit-based equation:

$$\text{Plasma volume (L)} = 0.07 \times \text{weight (kg)} \times (1 - \text{hematocrit})$$

CEA mass was estimated using the following formulae:

$$\text{CEA mass } (\mu g) = \text{CEA concentration} \times \text{plasma volume}$$

Statistical analyses

Statistical analyses were performed by using the SPSS 13.0 software. First, continuous variables, including age, WBC count, and hematocrit, were compared across BMI categories using ANOVA and X^2 for categorical variable smoking status.

Next, multivariate linear regression models were conducted to examine the associations of serum CEA concentration, BSA-based and hematocrit-based plasma volume, and CEA mass with BMI categories. As according to the Kolmogorov–Smirnov statistic the CEA and CEA mass were not normally distributed, the values were logarithmically transformed to attain a normal distribution before multivariate linear regression analyses. Binary logistic regression models were additionally conducted with nontransformed data by using normal weight (BMI ≤ 22.9) as the reference to assess the associations with overweight and obesity. In all multivariable analyses, age (years), smoking status, and WBC counts ($\times 10^9$) were considered as potential confounders.

Finally, we developed a theoretical formula for estimating plasma CEA concentration in high-BMI participants corresponding to a reference value in normal-weight males. We reconstructed the multiple linear regression model, including BMI categories. The estimates obtained were then back transformed for ease of interpretation. Associations with $P < 0.05$ were considered statistically significant.

Results

Table 1 presents the characteristics of the 1,915 males included in the analysis by BMI category. The mean (SD) age of men was 46.54 (12.42) years. Mean (SD) BMI were 24.75 (3.03) kg/m². More than half of all men were classified as overweight and 17.81% as obese. About half of the participants were smokers. Continuous variables, including age, hematocrit, and WBC counts, seemed to be higher in the obese compared with normal-weight males ($P < 0.05$).

Table 2 shows the relationship between CEA concentration, plasma volume, CEA mass, and BMI categories. The median CEA concentration was 1.57 ng/mL. The mean CEA concentration decreased from 1.64 ng/mL in normal-weight men to 1.46 ng/mL in obese men ($P < 0.001$). Means of estimated plasma volumes by using BSA- and hematocrit-based equations, increased with increasing BMI category, from 2.91 L in normal-weight men to 3.10 L in obese men, and from 2.63 to 3.06 L, respectively ($P < 0.001$). Estimated CEA mass, however, did not show a significant association with BMI ($P = 0.461$) when BSA-based equation was applied. Whereas when hematocrit-based equation was induced, CEA mass significantly increased with BMI ($P < 0.001$), with mean CEA mass

Table 1. Cohort characteristics of all men by BMI category

	BMI ≤ 22.9 kg/m² (n = 549)	BMI 23–27.4 kg/m² (n = 1,025)	BMI ≥ 27.5 kg/m² (n = 341)	P
Age (y; SD)	45.22 (13.38)	47.14 (11.62)	47.09 (12.78)	0.008
WBC count (10⁹/L; SD)	6.27 (1.67)	6.49 (1.54)	6.74 (1.66)	<0.001
Hematocrit (%; SD)	40.1 (2.22)	40.6 (2.15)	41.0 (2.13)	<0.001
Smoking status (n)				
Current smoker	315	589	212	
Former smoker	22	61	24	0.068
Nonsmoker	212	375	105	

values of 4.29, 4.55, and 5.14 μg across the three BMI categories ($P < 0.001$).

Results from logistic regression models were shown in Table 3. With normal-weight men as the reference group, the prevalence of the lowest CEA tertile was found to increase with BMI, with the OR of 1.35 [95% confidence interval (CI), 1.07–1.70] in overweight men and 1.40 (95% CI, 1.04–1.90) in the obese. Indeed, we found the ORs for the highest plasma volume tertile tended to get much higher in overweight and obese men by using both equations. The prevalence of the lowest or the highest CEA mass tertile, however, did not show a significant correlation with BMI ($P = 0.454$ or 0.549, respectively), when BSA-based equation was applied. When hematocrit-based equation was applied, a trend of an obviously positive correlation was observed between the prevalence of the highest CEA mass tertile and BMI ($P = 0.048$), in agreement with the findings from multivariate linear models as shown in Table 2.

For better understanding of the effect of obesity on serum CEA concentration, we developed a theoretical formula to assess CEA concentration in relation to BMI categories for predicting the practical influence of obesity on the interpretation of the serum CEA test. This model was used to estimate CEA values in obese people corresponding to a CEA value of 5.0 ng/mL (the most commonly used cutoff value for CEA screening) in over-

weight and obese people. We reconstructed the multiple regression model, including BMI categories. The following formula was obtained upon statistical analysis: $\log_{10}[\text{CEA}] = -0.035 + 0.016\,[\text{WBC}] + 0.005\,[\text{age}] + 0.051\,[\text{smoking status}] - 0.044\,(95\%\,\text{CI}, -0.019 \sim -0.069)\,[\text{BMI}]$. In this mathematical model, WBC count and age were continuous variables, smoking status was given a point from 1 to 3 (i.e., nonsmoker got point 1, former-smoker got point 2, and current smoker got point 3); BMI was given a point from 0 to 1 (i.e., normal-weight man got point 0 and overweight or obese man got point 1). Our model suggested that serum CEA of 4.52 (95% CI, 4.27–4.79) ng/mL in overweight or obese people were mathematically equivalent to 5.0 ng/mL in normal-weight men. When we put the predicted value back to our overweight or obese cohort, a specificity of 97.10% (96.4%–97.7%) was still obtained.

Discussion

In this study of nearly 1,915 healthy men with no clinical evidence of any cancer, after adjusting for potential confounding factors age, smoking status, and WBC count, men in the obese group had 11% lower serum CEA concentrations than normal-weight men, in line with the 3.8% decreased CEA concentration seen in another population-based studies of men without any cancer (9).

Table 2. Linear regression models: CEA concentration, plasma volume, and CEA mass according to BMI category

	BMI ≤ 22.9 kg/m² (n = 549)	BMI 23–27.4 kg/m² (n = 1,025)	BMI ≥ 27.5 kg/m² (n = 341)	P
Mean CEA concentration[a] (ng/mL; 95% CI)	1.64 (1.56–1.72)	1.49 (1.44–1.54)	1.46 (1.37–1.55)	<0.001
Mean plasma volume (L; SD)				
BSA-based	2.91 (0.17)	3.10 (0.18)	3.31 (0.22)	<0.001
Hematocrit-based	2.63 (0.24)	3.06 (0.27)	3.54 (0.37)	<0.001
CEA mass[a] (μg; 95% CI)				
BSA-based	4.75 (4.53–4.99)	4.62 (4.46–4.78)	4.81 (4.53–5.12)	0.416
Hematocrit-based	4.29 (4.09–4.50)	4.55 (4.39–4.71)	5.14 (4.84–5.46)	<0.001

[a]Adjusted for age, smoking status, and WBC count.

Table 3. Logistic regression models: adjusted associations of CEA, BSA-, and hematocrit-based CEA mass with BMI categories

	BMI $\leq$ 22.9 kg/m^2 (N = 549)	BMI 23–27.4 kg/m^2 (N = 1,025)	BMI $\geq$ 27.5 kg/m^2 (N = 341)	P
Prevalence of the lowest tertile of serum CEA level, n (%), and OR[a] (95% CI)				
	169 (30.8), 1.00 (reference)	356 (34.7), 1.35 (1.07–1.70)	117 (34.3), 1.40 (1.04–1.90)	0.026
Prevalence of the highest tertile of plasma volume, n (%), and OR[a] (95% CI)				
BSA-based	29 (5.3), 1.00 (reference)	344 (33.6), 10.44 (6.98–15.62)	252 (73.9), 62.87 (39.64–99.72)	<0.001
Hematocrit-based	13 (2.4), 1.00 (reference)	341 (33.3), 21.77 (12.34–38.41)	294 (86.2), 280.00 (148.16–529.11)	<0.001
Prevalence of the lowest tertile of CEA mass, n (%), and OR[a] (95% CI)				
BSA-based	185 (33.7), 1.00 (reference)	351 (34.2), 1.11 (0.88–1.40)	102 (29.9), 0.96 (0.71–1.30)	0.454
Hematocrit-based	213 (38.8), 1.00 (reference)	341 (33.3), 0.84 (0.67–1.05)	84 (24.6), 0.57 (0.42–0.78)	0.002
Prevalence of the highest tertile of CEA mass, n (%), and OR[a] (95% CI)				
BSA-based	185 (33.7), 1.00 (reference)	339 (33.1), 0.90 (0.72–1.13)	114 (33.4), 0.86 (0.64–1.16)	0.549
Hematocrit-based	160 (29.1), 1.00 (reference)	342 (33.4), 1.14 (0.90–1.43)	136 (39.9), 1.45 (1.08–1.94)	0.048

NOTE: BMI category as independent variable.
Reference group, normal-weight group.
[a]Adjusted for age, smoking status, and WBC count.

However, the cited study included only populations within a range of 0 to 5 ng/mL, which might be a reason for their findings of lower hemodilution effect.

Moreover, we observed obese men had greater plasma volume. When calculating CEA mass, i.e., the amount of CEA in the blood at the time of determination of CEA concentration, obese men had similar or higher CEA mass based on BSA- or hematocrit-based equation. Indeed, several small studies found that CEA concentrations increase acutely after dialysis (10, 11). This suggests that hemodilution from larger plasma volume may be responsible for the lower CEA values observed among obese men in our cohort. According to BSA-based equation for plasma volume calculation, we found that all men, regardless of BMI, had the same amount of circulating CEA, as reflected by the calculated CEA mass. When the hematocrit-based formula was applied, there was a significant trend for increasing CEA mass across BMI categories. Thus, we found no evidence that CEA mass was decreased among obese men. The greater CEA mass based on hematocrit suggests that obese men actually have more circulating CEA protein than do normal-weight men, but that this is diluted by their larger plasma volume.

The reason for the greater CEA mass is unclear. Because obesity is associated with some inflammation conditions and insulin resistance (12), which is also found in cancer development, we hypothesize two possible reasons:

First, obesity is known to promote an inflammatory state (13), and this proinflammatory condition may result in greater leakage of tumor marker into the serum (2). In our study, we confirmed that the circulating WBC count, a marker for systemic inflammation, was higher in obese men. We also observed both CEA and mass increased with increasing WBC count, even after age, BMI and smoking status were adjusted (data not shown). Second, insulin resistance might contribute to the increased CEA among obese men through insulin-like growth factor-I (IGF-I), because an antisense *IGF-I* gene that blocks the corresponding IGF sequences may be the reason for the decrease of CEA (14). Indeed, it was also reported that increased CEA was more commonly seen in men with metabolic syndrome or carotid atherosclerosis (15,16), which might indirectly support the hypothesized underlying mechanism.

Therefore, CEA may be affected in obese individuals by several factors, including but not limiting to hemodilution, inflammatory conditions, and insulin resistance. Interestingly, we found that though CEA levels were higher in overweight or obese men when compared with normal-weight men, no significant difference in CEA concentrations was found between overweight and obese men. The former result might suggest hemodilution predominates and the other two factors are rendered negligible. The latter result and some other conflicting findings might also be explained by this theory (17,18). In these studies no association was found between CEA concentration and BMI in healthy cohorts. It might be due to the fact that in these cohorts none of these factors could be rendered negligible.

Park and colleagues (3) reported that increased BMI might negatively affect the diagnostic precision of the CEA test in patients with colorectal cancer. They consider it may be necessary to interpret the CEA concentrations of obese patients in a manner distinct from that of normal-weight patients. Here, we also developed a theoretical formula to estimate CEA values in overweight and obese men corresponding to a CEA value of 5.0 ng/mL (the reference value of our laboratory) in normal-weight

subjects. The diagnostic accuracy of the CEA test might thus be improved by setting the reference value of the overweight and obese group about 4% to 15% lower than that of the normal-weight group.

Notably, in addition to the quantification of the effect of obesity on CEA concentration and the analysis of the possible underlying mechanisms, the third strength of our study is that both multivariate linear and logistic regression models were conducted to analyze the association of CEA level with BMI. Because logarithmic transformations conducted before multivariate linear regression analyses, might sometimes distort data (19), whereas dichotomization of the continuous dependent variable in the binary logistic regression models might yield a loss of information, our study fills in some of the blanks left by other studies in which linear or logistic regression analysis was applied alone. The additionally performed binary logistic regression analyses in our study using nontransformed data showed no conflicting results, though the corresponding significance does not seem to be as strong as that stated by using linear regression analyses with transformed data.

This study has several potential limitations. First, the reason for why the fact that CEA mass increased with increasing BMI was observed only when hematocrit-based equation was applied was not explained. We previously investigated the agreement between hematocrit- and BSA-based plasma volumes and found the dilution power of a plasma volume estimated by the hematocrit-based equation was much stronger than that calculated by BSA-based formula. Because of the absence of a plasma volume determined by "Golden criteria," we could not tell which equation is more suitable for clinical application. However, the discrepancies call for greater attention to further study on the problem (20). Second, because of the cross-sectional nature of the study, we cannot determine whether there is a causal or resultant relationship between the elevation of serum CEA and obesity. Third, we analyzed only

men in this study, because the number of female subjects who had a smoking history was much smaller during the study period. Fourth, in addition to cigarette smoking, age, and WBC count, serum CEA levels may increase under some other nonmalignant conditions, for example, hypothyroidism and etc. We did not include these disorders as confounding variables because their prevalence is considered to be very low among the study population.

In conclusion, CEA may be affected in obese individuals by several factors, including but not limiting to hemodilution, inflammatory conditions, and insulin resistance. The relationship between CEA concentration and BMI might be highly dependent on which factor or factors have been predominant. Obesity might be one of the factors that affect CEA value, leading to loss of diagnostic accuracy in the CEA test.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: F. Li
Development of methodology: F. Li
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Li, Z. Shen, Y. Lu, L. Wang, W. Song
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Li
Writing, review, and/or revision of the manuscript: F. Li
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Li
Study supervision: F. Li

References

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
2. Bãnez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007;298:2275–80.
3. Park JS, Choi GS, Jang YS, Jun SH, Kang H. Influence of obesity on the serum carcinoembryonic antigen value in patients with colorectal cancer. Cancer Epidemiol Biomarkers Prev 2010;19: 2461–8.
4. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
5. Grubb RL III, Black A, Izmirlian G, Hickey TP, Pinsky PF, Mabie JE, et al. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2009;18: 748–51.

6. Rundle A, Neugut AI. Obesity and screening PSA levels among men undergoing an annual physical exam. Prostate 2008;68: 373–80.
7. Sivanandam A, Siva S, Bhandari M, Menon M. Variance inflation in equential calculations of body surface area, plasma volume, and prostate-specific antigen mass. BJU Int 2008;102:1573–80.
8. Kaplan AA. A simple and accurate method for prescribing plasma exchange. ASAIO Trans 1990;36:M597–9.
9. Chang IH, Ahn SH, Han JH, Kim TH, Kim YS, Myung SC. The clinical significance in healthy men of the association between obesity related plasma hemodilution and tumor marker concentration. J Urol 2009; 181:567–72.
10. Lye WC, Tambyah P, Leong SO, Lee EJ. Serum tumor markers in patients on dialysis and kidney transplantation. Adv Perit Dial 1994; 10:109–11.
11. Docci D, Turci F, Pistocchi E. High levels of carcinoembryonic antigen (CEA) in the serum of uremic patients under hemodialysis treatment. Quad Sclavo Diagn 1984;20:435–9.

Li et al.

12. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J 2008;29:2959–71.

13. Das UN. Is obesity an inflammatory condition? Nutrition 2001;17: 953–66.

14. Zhang L, Li SN, Wang XN. CEA and AFP expression in human hepatoma cells transfected with antisense IGF-I gene. World J Gastroenterol 1998;4:30–2.

15. Kim KN, Joo NS, Je SY, Kim KM, Kim BT, Park SB, et al. Carcinoembryonic antigen level can be overestimated in metabolic syndrome. J Korean Med Sci 2011;26:759–64.

16. Ishizaka N, Ishizaka Y, Toda E, Koike K, Yamakado M, Nagai R. Are serum carcinoembryonic antigen levels associated with carotid atherosclerosis in Japanese men? Arterioscler Thromb Vasc Biol 2008; 28:160–5.

17. Herbeth B, Bagrel A. A study of factors influencing plasma CEA levels in an unselected population. Oncodevelopmental Biology & Medicine 1980;1:191–8

18. Lee JY, Lee HK, Lee DC, Lee JW. Serum carcinoembryonic antigen is associated with abdominal visceral fat accumulation in female Korean nonsmokers. PloS ONE 2012;8:1–6

19. Strimbu B. Correction for bias of models with lognormal distributed variables in absence of original data. Ann For Res 2012;55: 265–79.

20. Li F, Shen ZH, Lu Y, Yun JT, Fan YP. Serum prostate-specific antigen concentration and hemodilution among chinese middle-aged obese men: a hematocrit-based equation for plasma volume estimation is induced. Cancer Epidemiol Biomarkers Prev 2012;21: 1731–4.

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